Ureteric colic: evidence empowers responsible treatment

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The urological community has for decades pursued studies of so-called off-label drugs—ie, pharmaceutical agents used for an unapproved or unintended indication—for treatment of urolithiasis. But perhaps urologists should question why the pharmaceutical industry has not expressed an interest in drug development for this indication. Most urologists might have never even thought about the consequences, secondary effects, or possible (serious) adverse events that can occur during off-label use of a drug. However, the reason why urologists feel comfortable using α blockers for the treatment of urinary stones, for example, could be that both the American Urological Association and European Association of Urology guidelines include α blockers in their treatment recommendations.[1,2]

Use of α blockers to facilitate stone passage has increased in popularity, even though efficacy has only been supported by level 2a evidence. In the absence of a methodologically good and well powered randomised controlled trial (RCT), clinicians often have to turn to evidence from less reliable sources, such as single-centre comparative studies, registries with matching groups, non-placebo-controlled or unpowered RCTs,[3] and (as a last resort) meta-analyses.[4] Sophisticated statistical tests are also needed to assist what should be straightforward analyses.

In *The Lancet*, Robert Pickard and colleagues[5] present the results of their three-group, randomised, placebo-controlled trial of medical expulsive therapy (tamsulosin 400 μg or nifedipine 30 mg) in adults with ureteric colic. 1167 patients were randomly assigned, and in terms of the trial's primary endpoint—the proportion of patients not needing further intervention for stone clearance within 4 weeks—no difference was reported between treatment groups (303 [80%] of 379 participants in the placebo group did not require further intervention, compared with 307 [81%] of 378 participants in the tamsulosin group [adjusted risk difference 1·3%, 95% CI −5·7 to 8·3] and 304 [80%] of 379 participants in the nifedipine group [0·5%, −5·6 to 6·5]). This study therefore removes, beyond any reasonable doubt, any positive expectations with respect to α blockers in the treatment of ureter stones. Furthermore, because the trial had three treatment groups, the findings eliminate doubt about whether one active drug might be more powerful than the other.

Several things can be learned from Pickard and colleagues' study[5] and its findings—the main one being the important role of quality of evidence and reporting of outcomes. It raises the question of whether well powered RCTs are indeed the ultimate way to prove efficacy of a specific treatment. Taking the accompanying study as an example, the answer is indisputably yes. When planning such a trial, the investigators have to obtain insight from case series or registries, but definitive evidence must come from RCTs. A power calculation is a prerequisite of any well designed RCT, but was either missed or not reported in a recently published RCT on ureteral stones.[6] Either by omission or absence, the lack of properly undertaken or reported methods raises concerns about the usefulness of the data, and might lead to incorrect conclusions. Simply put, the evidence in all studies other than properly designed and powered RCTs is just not robust enough to use as the basis for treatment decisions.

The collection and reporting of evidence comes with responsibilities, and urological societies are likely to be

Coloured urogram showing ureter blocked by stone

instrumental in improving the process. Encouragingly, the Endourological Society has created the Clinical Research Office of the Endourological Society (CROES).[7] Through the global network of CROES, several registries have been started, followed by large-scale RCTs.[8,9] The conclusions from these studies emphasise that the responsibility to provide reliable evidence requires input from stakeholders in urology, industry, and regulatory agencies around the world.

But other lessons too can be learned from Pickard and colleagues' study. Even in a well designed and undertaken trial, investigators need to improve standardisation of patient outcome reporting. Although attempts have been made to improve reporting of clinical research, international standards to define patient outcomes are limited.[10,11] Opondo and colleagues[12] were the first to propose recommendations to define outcomes in patients treated for renal stones. Standardised reporting of outcomes is the first step towards improving scientific knowledge; it forms the basis for comparison between and among studies, and ultimately should allow for meaningful systematic reviews and meta-analyses.

The primary outcome in Pickard and colleagues' study was the proportion of participants in each group who did not need further intervention for stone clearance within 4 weeks of randomisation. Although this outcome is possibly clinically relevant, the question arises as to whether findings would have been the same if the primary outcome of the study had been confirmed stone expulsion or absence of a stone on imaging. To help compare results between different studies, outcomes should be defined and the same definitions used across different studies.

Critical appraisal of research methods and findings is a demanding task for urologists to undertake when deciding on the best treatment for their patients, but it is very rewarding when successful. A thoughtful research process, involving formulation of a meaningful research question and proper methodology, reporting, and critical appraisal, will ultimately allow the best quality of care to be delivered to patients.

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Withdrawal from methadone in US prisons: cruel and unusual?

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In the USA, as in many other settings, the main societal response to the harms of opioid addiction is arrest and imprisonment. The so-called war on drugs has contributed to an era of mass incarceration, in which about one in every 100 US citizens, almost all poor, many from racial minority groups and many who use illicit drugs, are currently detained in jails or prisons.[1] The USA not only has the world's highest rate of incarceration, but treats opioid-addicted prisoners very differently from those in prisons in other countries. Unlike other serious chronic conditions such as cancer, diabetes, or HIV/AIDS, individuals with opioid dependence will often have their medically effective treatment—such as methadone, the standard